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ABSTRACT

The paper reviews research on effects of metal pollutants on behavioral disorders in children. Methodological programs of studies conducted in the 1970's are described. Research since 1980 is then addressed in terms of general population studies and studies of behaviorally disordered populations. Findings of research on the latter subject group are examined in criteria for establishing causative relationships: (1) strong associations; (2) consistency of the observed association; (3) dose-response relationships; and (4) biological plausibility. It is concluded that, despite methodological flaws, the studies show an association of behavioral deficits with low or moderate metal levels. A reference list containing 61 entries concludes the report. (CL)

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EXPOSURE TO METAL POLLUTANTS AND BEHAVIORAL DISORDERS IN CHILDREN: A REVIEW OF THE EVIDENCE

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Exposure to Metal Pollutants and Behavioral Disorders in Children:

A Review of the Evidence

Introduction

It is medical and scientific consensus that metal pollutants are neurotoxins, and that children who survive the effects of metal poisoning are often left with permanent neurological sequelae, including severe behavioral disorders /1/. A source of considerable debate, however, is whether lesser levels of metals, considerably below those associated with metal poisoning are a causative factor in neurological dysfunctions, including behavioral disorders. The empirical foundation of this debate is (1) the variety of studies conducted since the early 1970's demonstrating significant correlations between low and moderate asymptomatic lead levels and childhood behavioral dysfunctions, and (2) the much fewer studies linking low-moderate levels of mercury, cadmium, arsenic, and aluminum hitherto regarded as safe to behavioral deficits in children.

Official recognition of this issue can be seen in the steadily downward revision by health authorities of the threshold level of lead in the body. In the 1960's, using blood lead as the index of exposure, the threshold level was considered to be 60 ug/dl of blood. The United States Surgeon General then recommended in 1970 that 40 ug/dl be the threshold level. In 1975 the figure was revised downward to 30 ug/dl, but the United States Center for Disease Control cautioned when proposing this new figure that, at that level, there is a danger of clinical lead poisoning. Some authorities now assert that 20 ug/dl represents an unsafe and harmful level.

The purpose of this paper is to critically review the evidence stemming from (1) reported dose-response measures in general populations and from (2) reported differences between metal levels in groups of behaviorally disordered children compared to normal controls. The review's focus will be on studies conducted since 1980 with the exception of Needleman and others' important 1979 study of dentine lead and psychologic deficits in suburban Boston area school children. This focus has been selected because of serious methodological weaknesses associated with studies prior to 1980.

Methodological Considerations

Although the majority of the studies of the 1970's demonstrated low significant correlations between increased metal uptake and behavioral deficits /3,4,5,6,7,8/ or demonstrated data trends in the expected direction /9,10,11,12,13/, doubts remained regarding the causal inferences of these studies because of failure to deal with one or more of the following crucial methodological considerations. First, many of the studies had selection bias as the result of (1) using clinic samples or volunteer subjects, (2) the differential loss of subjects, and/or (3) failure to obtain systematic data on all individuals in the study. Second was the problem of obtaining valid and sensitive measures of children's behavior. Some studies relied on rather crude and poorly validated checklists, while others used standardized behavioral scales. Clearly the former represented less sensitive measures of behavioral performance and were more likely to miss deficits which were restricted to certain types of behavioral performance. Additionally, none of the studies of the

1970's used applied behavior analysis measurements, nor were self-ratings, peer ratings, or parent ratings of behavior employed.

A related measurement issue is that studies which focused on differences between behaviorally disordered groups of children and controls were limited by the problems associated with the diagnostic subclassifications of childhood behavioral disorders. There is a great deal of variability among clinicians in their choice of categories for children who exhibit given behavioral characteristics, e.g., hyperactive, learning disabled, conduct-disordered /14/, and the absence of empirically derived subcategories to which children's disordered behavior can be reliably and efficiently assigned is a drawback in drawing inferences between specific behavioral correlates and membership in a behaviorally disordered group.

Third, the majority of research designs used single blood lead concentrations as the index of exposure, often with measures obtained several years prior to the behavioral assessment of the children. Blood lead is an index of very recent exposure only, and it may return to normal levels even though the exposure was excessive. This is possible when clearance of lead from the blood into long-term storage compartments of the body, such as bone, kidney, and liver, can occur rapidly relative to overall body excretion rates. Errors are likely to occur, therefore, if blood lead is relied on to classify subjects after exposure has abated. Only in situations in which the metal intake is continual and relatively similar over a period of time comparable with blood-clearance rates may blood concentrations be a steady-state measure of overall body burden.

Repeated measurements of blood lead over time would meet these objections, but are very rarely available. To meet this problem, research in the 1980's has relied in large part on dentine or tooth lead or scalp hair metal concentrations since they reflect the long-term overall body burden /15,16,17/.

Fourth, there was the problem of statistically controlling for possible confounding variables (e.g., psychosocial, genetic, and perinatal influences) that could masque the relationship between metal exposure and behavioral performance. Even if it can be shown that children exposed to metals are behaviorally disordered, there is still the question of whether the association represents a consequence of metal exposure or whether both increased metal levels and the behavioral deficit are due to some third factor. To clarify this issue, consider the following two examples. First, studies have shown that children of lower socioeconomic status tend to have higher lead levels than those from more privileged backgrounds. The problem here stems from the fact that both social class and lead levels are associated with differences in behavioral performance. In other words, all three sets of variables are interlinked. Clearly, one must statistically control for this overlapping relationship between lead level, social class, and behavior. Secondly, pica the ingestion of nonnutritive substances, e.g., paper, dirt, paint, is a major source of lead ingestion in children and occurs more often in behaviorally disordered children /18/. Here one is faced with determining whether increased metal levels result in behavioral deficits or whether disordered behavior leads to increased metal levels.

Multivariate statistical techniques have been developed to partial out the influence of social class, pica, and other confounding variables prior to examining dose-response measures, but the vast majority of studies of the 1970's relied on univariate analyses and did not statistically control for confounding variables.

Finally, studies of the 1970's used univariate statistical techniques that were relatively insensitive for evaluating the effects of continuous variables such as metal exposure. Any arbitrary groupings of subjects according to metal burdens (e.g., 2-8.5 ppm equals "low lead" group and 20-40 ppm equals "high lead" group), as required in traditional analysis of variance, results in a loss of information. For instance, any behavioral changes that might be present within a specific exposure group (e.g., 2-8.5 ppm) would be obscured by averaging all data within that group. The statistical model chosen has considerable effect on the conclusions drawn from a specific data set. In particular analysis of variance tends to suggest an arbitrary threshold view of toxicant effects based on the comparison of discrete means, while the linear regression model tends to suggest a continuum view based on the utilization of a continuous range of burden values.

The preceding five methodological considerations will be applied to the present review of research conducted since 1980 along with Needleman's 1979 study. These studies have been divided into two categories: (1) general population studies and (2) studies of behaviorally disordered populations.

General Population Studies

Needleman and others /2/ examined the behavioral performance of children in the general population with "high" and "low" lead levels as assessed by dentine analysis. Shed deciduous teeth from 70% of 3,329 children attending first and second grade classes in two white working class towns near Boston were collected. A mean lead level of 14.03 ppm (SD 9.22) was found. Fifty-eight children with a level above 20 ppm were classified as "high lead" and 100 with a level below 8.5 ppm as "low lead." It should be pointed out that a cut-off point of 20 ppm is only 0.65 of a standard deviation above the mean. The two groups were invited for neuropsychological evaluation. The mother accompanied the child to the testing site and filled out a lengthy questionnaire which scaled 39 non-lead covariates of potential influence on development. The two groups were compared by univariate t-tests, and covariates that differed at $p<0.1$ were entered into biostatistical analysis and thus controlled. Family size, mother's age at subject's birth, mother's education, father's social class, and parental IQ were entered into the analysis of covariance.

High and low lead subjects were then evaluated by their teacher on an eleven-item, forced choice questionnaire which evaluated general classroom behavior, with particular focus on attention. The data showed that high lead children were rated significantly lower than low lead children on 10 of the 11 items, and these differences persisted after partialling out the contributions of psychosocial variables that differentiated between high and low lead subjects.

It was subsequently found that 69% of the low overall classroom behavioral performance in the children with high lead could be attributed to their lead exposure /19/.

Bellinger et al. /20/ conducted a follow-up study and measured on- and off-task behavior of a sample of these 158 children (N = 41). The data was based on 144 7-second observation periods for each of 41 children during quiet academic work, and off-task behaviors were assigned to one of eight categories. The results showed that high lead children (N = 13) displayed the most off-task behavior in all eight behavioral categories ($p<.0002$) when compared to middle lead subjects (N = 13) and low lead subjects (N = 15).

In addition to the preceding data teacher ratings were available for 2,146 subjects for whom a dentine lead level was on file. The subjects were classified according to increased dentine lead levels in six classes arranged to give a symmetrical distribution around the mean, and the proportion of negative teacher reports was calculated. A strong dose-response relationship for all 11 items was seen.

Although limited by univariate analyses, Needleman's study appears to be a well planned, detailed, and systematic study. The implication is that children with high lead differ from those with low lead in classroom behavior. The applied behavior analysis data of Bellinger et al. /20/ also supports this inference. The consistent dose-response relationship with respect to the teachers' behavioral ratings for the 2,146 subjects also strengthens the causal inference, although the force of the inference is reduced by

the fact that it was not possible to control in the analysis for psychosocial factors (because such data were available only on the high and low lead groups and not on the population as a whole).

Lansdown et al. /21/ examined the relationship between blood lead concentrations and behavior in 166 London children who lived near leadworks. The range of blood lead concentrations was from 7 to 32 ug/dl with a mean of 13.52 and a standard deviation of 4.13. Teachers were asked to complete three behavior rating scales on each child, the 11-item forced choice scale used by Needleman et al. /2/, the 26-item Teacher Rating Scale B2 /22/, an indicator of emotional and behavioral difficulty, and the 40-item Conner scale /23/, a measure of hyperactivity. Behavioral ratings were completed in the summer term of 1980, some 9 to 12 months after the blood samples had been taken. The group was split into four quartiles according to lead levels. The pattern of results for the Needleman scale were very similar to those in Needleman et al.'s study. In 5 of the 11 items, the associations between blood lead level and behavior rating were statistically significant. In a further 4 items, children with blood lead levels of 12 ug/dl and below received fewer negative ratings than those above the median level.

When the top 50% of the lead distributions (i.e., 13 ug/dl and above) were compared with the remainder on the Rutter Teacher Rating Scale, the higher lead group was more often deviant on 20 of the 26 items. For only two items--"squirming" and "fights"--was this difference statistically significant at the .05 level; in five others the difference was significant at the .10 level. On the

Conner scale children in the top 50% of the lead distribution were rated as more deviant on every subscale. These differences reached statistical significance ($p<.05$) for Conduct Problems, Inattentive-Passive, Tension-Anxiety, Hyperactivity, and Total Score.

Lansdown et al.'s findings on behavior broadly replicate Needleman's findings. On the same items, there are indications of a dose-response relationship between increasing lead levels and teacher reported deviant behavior at blood lead levels far below 30 ug/dl, the threshold above which children are presently considered to have an elevated body burden. Furthermore the associations between lead levels and performance on the Rutter and Conner scales provide harder evidence of an association between low lead levels and behavioral disorders.

These findings require caution in their interpretation, however, because of various considerations. One limitation is that social class, pica, and other psychosocial variables were not used as covariates in the analysis. Second, the investigators relied on a single estimate of blood lead taken some 9 to 12 months prior to behavioral testing and as such may not be representative of the children's exposure at the time of the behavioral assessment.

In a well planned and well analyzed study, Winneke et al. /24/ analyzed the shed teeth of 317 school children living in a lead smelter area in Stolberg, Germany. The range of tooth lead concentrations was from 1.5 to 38.5 ug/100 ml with a mean of 6.0 ug/100 ml. More than 50 possible confounding variables were collected on the social environment, the family, and the case history of the child.

Only two, duration of partuition and sociohereditary index (mother and father's occupation and type of school attended) correlated significantly with lead levels and were entered into a stepwise regression analysis with tooth-lead being entered as the last step. Behavior ratings given by the mothers and teachers, using almost identical 11-item 7-point rating scales, emphasized different aspects of attention, organization, and endurance displayed by the children when doing homework or in the classroom, respectively. Borderline ($p<.10$) to significant associations were observed between 4 of the 11 single-item mother ratings and tooth-lead levels, after correcting for covariates. The proportion of variance accounted for by the four significant items ranged from 1.7% to 5.3%. The associations, although positive for all 11 items, were weaker for the teacher ratings, which exhibited a much stronger relationship with sociohereditary background than did those of the mothers.

These findings largely agree with Needleman and Lansdown's findings, as far as content is concerned but are at variance with their findings, if the source of information is considered. Whereas teacher ratings, without being corrected for socio-economic backgraound did produce pronounced dose-response characteristics in the Boston and London studies, Winneke et al.'s data demonstrated that the teachers--unlike the mothers--were influenced mainly by the knowledge of the socio-hereditary background of the child. Mother ratings, on the other hand, exhibited significant or near significant association with increasing tooth-lead concentrations for the following items: "distractible," "ignorant about instructions or

homework," "restless," and "poorly informed."

Marlowe et al. /25/ examined hair trace metal concentrations of lead, arsenic, mercury, cadmium, and aluminum and metal interactions in 108 randomly selected elementary age children from two rural cities in Wyoming. Scalp hair samples were analyzed for trace metal content by Doctor's Data, Inc., a Center for Disease Control licensed laboratory in West Chicago. Each subject was rated by his/her teacher on the 50-item Walker Problem Behavior Identification Checklist /26/ which yields five subscale scores. Factorial analysis of the five subscales revealed that only two, Acting-Out and Distractibility, were independent subscales /27/. Parents were surveyed via questionnaire to control for 11 confounding variables (e.g., social class, pica). The children's hair metal means were well within the normal range of hair metal values reported by the laboratory (lead $\bar{X}$ = 6.65 ppm, SD = 3.08, normal range = >15.0; arsenic $\bar{X}$ = 2.94, SD = 1.41, normal range = >7.0; mercury $\bar{X}$ = 0.99, SD = 0.44, normal range = >2.5; cadmium $\bar{X}$ = 0.64, SD = 0.41, normal range = >1.0; aluminum $\bar{X}$ = 9.41, SD = 4.88, normal range = >30.0) /28/.

A hierarchical multiple regression analysis was conducted on the Walker scales. The independent variables were entered in a series of three sets in the following order: (a) sex, age, covariates, (b) the five metals, and (c) the interaction of every pair of metals. Metal interactions were assessed because it has been hypothesized that metal interactions may have a negative synergistic effect which increases the total toxicity of the system /29/.

For the 13-item Acting-Out subscale, 9% of the variance was

explained by the set of five metals ($p<.10$) and another 16% by metal interactions ($p<.01$). Of the 9% of the variance due to the metal set, over 5% was accounted for by lead ($p<.05$). For the metal pairs, 9% of the variance was accounted for by the interaction of lead with cadmium ($p<.001$) and over 2% by the interaction of arsenic-aluminum ($p<.10$).

For the 16-item Distractibility subscale, 18% of the variance was explained by the set of metals ($p<.01$) and an additional 4% by the set of metal interactions ($p>.10$). Of the 18% of the variance attributable to the metal set, lead accounted for over 9% ($p<.001$), mercury accounted for 5% ($p<.05$), and aluminum accounted for 4% ($p<.05$).

For the 50-item Walker Total Scale score, 13% of the variance was explained by the set of metals ($p<.01$), with lead accounting for almost 10% ($p<.001$). Metal interactions accounted for 10% of the variance with lead-cadmium accounting for 4% ($p<.01$) and lead-arsenic accounting for 3% ($p<.05$).

Marlowe et al.'s results are important in terms of (a) the demonstration of associations between behavioral deficits and various toxicants at low levels, and (b) the finding that metal interactions are associated with behavioral deficits, beyond the contributions of a metal set.

Caution is required in the interpretation of these results for several reasons. First, the sample size was relatively small and 28 of the 108 subjects had missing data on one or more covariates. Second, the study is weakened by rather limited data on psychosocial

and genetic covariates. There were no measures of the "home care-giving environment" or parental IQ, both of which have been found to be significant covariates in lead-neuropsychological studies. As such, the amount of variance attributed to the metals is most likely overestimated. Third, excluding lead, little is known about the low dose effects of other metals or the interactions of metals in young children, and their functional significance is quite uncertain. Nevertheless, these data are consistent with a continuum model of metal neurotoxicity, i.e., that behavioral deficits are proportional to body metal burdens.

Milar et al. /30/ correlated blood lead levels in children of battery workers in North Carolina with activity levels as measured by the Conner and Weiss-Peters parental rating scales as well as observations of playroom behavior. No differences according to blood lead levels were found for any of the measures of hyperactivity, prior to controlling for confounding variables. The findings are important, but it may be the lack of difference reflects the invalidity of the hyperactivity measures in the age group studied. The validity of rating scales with very young children is weak /31/, and 54 of the 88 subjects were under three years of age.

Marlowe et al. /32/ examined hair levels of lead, arsenic, cadmium, mercury, and aluminum in 64 elementary age Native American Indian children on a Wyoming reservation in relation to their ratings on the Walker Problem Behavior Identification Checklist. Of the five metals, only aluminum levels correlated positively ($p<.05$) with Walker Total Scale score after correcting for age, sex, social class,

and pica. The biological significance of these findings is not clear. Recent findings indicate that aluminum binds to DNA, deposits in abnormal neurofibrillary tangles in the brain, may be a cause of these abnormal changes, and has been linked to three types of dementia diseases: senile dementia, parkinsonism dementia, and dialysis dementia /33/. Previous studies have also linked increasing hair aluminum levels with deficits in visual-motor performance /34,35/ and learning disabilities /36/.

The meaning of these findings is limited by several other considerations: (a) the small sample size, (b) the possibility of undetermined genetic differences in Indian children's response to metal uptake, (c) the cultural bias of using a classroom behavior rating scale validated on non-Indian children, and (d) lack of psychosocial data on subjects.

Behaviorally Disordered Populations

Hansen et al. /37/ determined hair lead concentrations in 20 hyperactive children drawn from a children's psychiatric hospital in Risskov, Denmark, and a control group matched according to age, sex, social class, place of domicile, and father's occupation. A significantly higher ($p<.05$) lead level was found in the hyperactive group ($\bar{X}$ = 13.9 ppm, SD = 6.9) compared to the controls ($\bar{X}$ = 6.9, SD = 0.83), although lead levels in both groups were within the normal range of hair-lead values reported in the literature (>15 ppm). The findings of increased lead uptake in the pathological group is suggestive, but the meaning of the difference is weakened by failure to obtain a measure of pica on the subjects.

Kracke /38/ compared hair element content in 40 behavior disturbed children drawn from special education classes and mental health programs and 77 controls in two Kansas counties. The disturbed children were either classified psychotic (N = 20) or neurotic (N = 20) by the author in a rather idiosyncratic way. Large significant differences were found between the groups for several nutrient elements as well as lead ($p<.05$). The neurotic group had significantly higher hair-lead levels ($\bar{X}$ = 14.65 ppm, SD = 9.90) than the psychotic group ($\bar{X}$ = 9.95, SD = 5.02) or control group ($\bar{X}$ = 5.82, SD = 1.98).

This study generally replicates Hansen et al.'s /37/ findings of higher lead levels in a behaviorally disordered group, but the study is weak in numerous respects. Perhaps the most important sources of bias are (1) very little is known about the psychosocial backgrounds of any of the children, (2) no data is available on the presence of pica, (3) nutritional status was unequally represented across the three groups with the control group having a larger percentage of its members with nutritionally adequate diets, and (4) the paper does not give adequate operational definitions for neurotic or psychotic.

Marlowe and Errera /39/ determined hair lead levels in a group of children in three rural Tennessee counties (N = 26) nominated by classroom teachers as having severe behavioral problems and in a control group (N = 29) matched for sex, ethnic group, pica, and social class. Children were rated by teachers on the Walker Problem Behavior Identification Checklist. The group of behavior problem

children were higher ($p<.05$) in hair-lead ($\bar{X}$ = 11.61 ppm, SD = 7.65) than the controls ($\bar{X}$ = 6.52, SD = 2.62), although the hair lead values of both groups were within the normal range of hair-lead values. Six of the behavior problem children were elevated in lead (>15 ppm) compared to none of the controls. The lead levels of all 55 children were associated ($p<.05$) with teacher ratings on the Acting-Out subscale, the Distractibility subscale, and Walker Total Scale score.

The results of this study are broadly in keeping with the findings of Hansen et al. /37/ and Kracke /38/, and they are not open to the objection that high lead levels arose in disordered children because of pica. The teacher-rating findings also correspond to findings of previously reviewed general population studies.

These findings are difficult to evaluate, however, because of serious methodological weaknesses. First, the control group was two years younger on the average ($p<.05$). Second, there is the problem of sample bias due to teacher-nominated subjects. Third, the only psychosocial variable obtained on the children was social class, and fourth, teacher-ratings were not corrected for age, sex, or social class.

Marlowe et al. /40/ determined hair levels of lead, arsenic, cadmium, aluminum, mercury, nickel, and beryllium in emotionally disturbed children (N = 22) from two Wyoming school districts and in a control group (N = 25). The groups were matched for age, sex, social class, pica, and ethnic group distribution. Each child was rated by their classroom teacher on the Walker Problem Behavior Identification Checklist. The emotionally disturbed group was

significantly higher ($p<.05$) in lead ($\bar{X}$ = 15.31 ppm, SD = 16.11) than the control group ($\bar{X}$ = 8.64, SD = 2.17). The disturbed group's large standard deviation for lead was due to 6 of the 22 disturbed subjects showing elevated hair-lead concentrations (elevated range = 15 ppm to 81 ppm). The disturbed group's arsenic, cadmium, and aluminum levels correlated with Walker Total Scale score after correcting for social class ($p<.05$). No metals correlated with Walker Total Scale score in the control group.

The findings are provocative and potentially important, as they (1) support the suggestion that increased lead exposure leads to significant behavioral deviance, and (2) implicate other metals in classroom behavioral deficits. Conclusions about the study must remain tentative, however. The study relied on univariate analyses and did not partial out the effects of sex, age, or other metals in examining relationships between individual metals and teacher-ratings. Furthermore, the only psychosocial data obtained on the groups was father's occupation and level of educational attainment, so there may not have been matching on all relevant variables.

Walsh /41/ compared hair elements in 24 delinquent violent male children with those of 24 nonviolent male siblings. All 24 violent children were elevated in lead and cadmium as well as iron and calcium, while none of the nonviolent siblings exhibited these patterns. The radical differences in element levels that characterized the groups was attributed to a chemical imbalance or metabolic disorder.

A second phase of the study examined hair element content of 96

violent youth and men and 96 nonviolent counterparts matched for age, sex, race, social class, and place of domicile. Ninety-two of the 96 violent subjects exhibited elevated lead and cadmium levels compared to 3 of the controls. Unfortunately, the author does not report the means and standard deviations of the element levels for the groups in either study phase, and this omission makes the impressive findings impossible to evaluate.

Marlowe et al. /42/ determined hair concentrations of lead, arsenic, mercury, cadmium, and aluminum in emotionally disturbed children (N = 37) in three Wyoming counties and in controls (N = 107). Each subject was rated on the Walker Problem Behavior Identification Checklist. The groups did not differ in age, pica, or ethnic group membership, but the disturbed children were of a lower socioeconomic status ($p<.05$) and a greater percentage of its members were male ($p<.05$).

The emotionally disturbed group had a mean hair lead of 10.78 ppm ($p<.001$) and mean hair mercury of 1.30 ppm ($p<.01$) compared to the controls' mean hair lead of 7.02 and mean hair mercury of 0.95. Six of the disturbed subjects were elevated in hair lead (>15 ppm) and three were elevated in hair mercury (>2.5 ppm). A discriminant analysis was performed to determine to what extent the metals and their interactions could separate the two groups after controlling for age, sex, and social class. Over 16% of the variance between groups was accounted for by the set of covariates. The addition of lead to the discriminant function accounted for 10% of the variance ($p<.01$) beyond the covariates. Almost 7% ($p<.01$) was uniquely attri-

buted to mercury, over 5% ($p<.01$) to arsenic, and about 2% ($p<.05$) to the interaction of mercury-aluminum after controlling for the metal set. Standardized discrimimant function coefficients revealed that the most important variable in the discriminant function was lead (.70), followed by mercury (.54), arsenic (-.51), social class (.50), sex (.38), aluminum-mercury (.34), and age (.33). On the basis of the discriminant function 78% of the 144 subjects were correctly classified as disturbed subjects or nondisturbed controls.

A hierarchical multiple regression was conducted on the Walker scales. The independent variables were entered in a series of three steps in the following order: (a) age, sex, social class, (b) the set of five metals, and (c) the interaction of every pair of metals. For the Acting-Out subscale, over 14% of the variance ($p<.01$) was explained by the metal set with mercury (8%, $p<.01$) and lead (6%, $p<.01$) being the major contributors. Eight percent of the variance was explained by the metal interactions ($p<.10$), with the interactions of arsenic-aluminum, lead-aluminum, and cadmium-aluminum being significant ($p<.10$).

For the Distractibility subscale the metal set accounted for 18% of the variance ($p<.01$) with lead accounting for 15% ($p<.01$) and aluminum over 2% ($p<.05$). None of the metal interactions were significant.

For the Walker Total Scale score the metal set accounted for 20% of the variance ($p<.01$) with lead explaining 12% ($p<.01$) and mercury 7% ($p<.01$). About 5% of the variance was accounted for by the set of 10 metal interactions. This incremental increase was nonsignificant.

Altogether, this seems to be a well analyzed study, and clearly the results demand serious consideration. The implication is that emotionally disturbed children differ significantly from nondisturbed controls in their metal uptake. The inference of a causal relationship is strengthened by the finding of a consistent dose-response relationship with respect to the teachers' classroom behavior ratings, an association that is apparent both above and within the accepted range of hair metal levels.

As with all of the previously reviewed studies of behaviorally disordered populations, there is inadequate control for psychosocial variables, e.g., quality of the home caregiving environment, maternal IQ. As such, there are considerable reservations about the study, but none of these are sufficient to invalidate the findings.

Effects and Implications

Bradford Hill /43/ elaborated some of the requirements for establishing causative relationships with respect to biological processes. Not all of these are germane to the social sciences, but they provide a framework within which to summarize the contributions of recent studies to the question of whether low metal exposure causes behavioral disorders.

Bradford Hill posited that causality is more likely where the association is strong. The studies reviewed here point to low or moderate statistically significant correlations between low metal exposure and behavioral deficits. However, behavior is multifactorally determined, as there are a large number of genetic and environmental determinants of behavior, and for low metal exposure

to account for even 5% of the overall variance is important. The magnitude of the associations vary from study to study, but one should expect this due to (1) differences in measurements of metals, i.e., tooth, dentine, blood, and scalp hair specimens, (2) the variety of behavioral measures used, ranging from crude checklists to standardized teacher-ratings, (3) varying degrees of statistical control for confounding variables, (4) different data analysis approaches, and (5) different sample characteristics.

A second criteria is the consistency of the observed association. Five of the six general population studies conducted in the 1980's are consistent with a continuum model of metal neurotoxicity, and all six studies of behaviorally disordered populations reported increased exposure levels that do not produce overt symptoms of metal poisoning and that are unlikely to be detected. These observations replicated by independent investigators in different cultures lend support to the causal inference.

A third criteria is dose-response relationship. In other words one should expect that behavioral performance is affected in a graded manner across the entire range of exposure. With respect to most investigations there is evidence of a dose-response relationship, but it is difficult to measure such relationships across studies because of aforementioned differences in measures of metals and behavior and differences in sample characteristics and research designs. The only reasonable conclusion is that methodological difficulties preclude dose-response comparisons across studies. However, the data on dose-response relationships within studies, in

general supports the causal inference.

A fourth criteria is biological plausibility. The evidence from experimental animal studies supports the causal inference, as the literature shows that systematic administration of metals to rodents and subhuman primates produces neurochemical, anatomical, and behavioral deficits. This evidence regarding low lead has been succinctly reviewed by Silbergeld /44/.

The coherence of the human evidence is less certain. Nevertheless, evidence is accumulating of low level metal-related alterations of the peripheral and central nervous system of adults and children /45,46,47,48,49,50,51,52,53/. The aggregate of the data suggests a continuum of nervous system effects across a broad range of lead and cadmium burdens with no obvious threshold effect. Low levels of other metals, e.g., mercury, aluminum, arsenic, have not been studied in relation to CNS impairments in sample populations of the young.

Research Implications

In future research it will be important not only to try to replicate existing findings and to correct the faults of earlier studies, but also to plan new research strategies. Three issues merit brief discussion in this regard.

First, future research strategies should focus on the contributions of metal sets and metal interactions to behavioral deficits. Although there are important differences between metals and their uptake and distribution by the body and their toxic effects on metabolism, there are also important similarities between the

incidence and acute effects of metals. Metals often occur together in the same ore bodies /54/, and their concentrations in blood and hair often show strong positive correlations /25,35,42,55,56/.

The overt symptoms of high doses of various metals are also similar, e.g., deficits in visual and auditory functions, impaired fine muscle control and coordination, emotional lability, and behavioral reactivity /57/. As such, it is possible that a greater amount of behavioral variance could be explained by looking at sets of metals and their interactions. The data of Marlowe and colleagues supports this observation.

Given the multicollinearity of metals, it is also possible that some of the deleterious effects attributed to lead in previous correlational studies, may instead be due to other metals. Future investigations should partial out the contributions of other metals, prior to examining dose-response measures.

Although metal interactions accounted for a significant amount of the Walker Total Scale variance in only one of the two studies measuring this relationship, previous studies have also linked metal interactions to decreased visual-motor performance /35/ and decreased reading and spelling achievement /58/. The biological import of metal interactions is most uncertain, however, and at present there are no health standards for exposure to combinations of metal pollutants.

A second issue is metal and nutrient mineral ratios. There is a great deal of evidence that indicates that nutritional status can influence susceptibility to metal toxicity. Deficiencies in calcium, iron, zinc, and phosphorous are all known to increase susceptibility

lead intake from all sources, family education for all, correction of nutritional deficiencies where they exist, and careful monitoring of the child will usually suffice in reducing undue lead absorption.

Conclusions

In sum, the body of studies reviewed here present overall a consistent array of data that behavioral deficits are associated with low or moderate metal levels, methodological difficulties of the studies notwithstanding. Well controlled studies have found effects that are clearly significant (i.e., "real") in general populations, and increased lead levels are common to all of the studies of behaviorally deviant populations.

The effects of low metal exposure, though significant and important, appear to be subtle and not easily discernible. These effects may be of additional importance for several reasons. First, the effects may signal the early stages of an ongoing toxic process that becomes more disabling with age. Second, a metal pollutant that produces subtle behavioral effects in many children may produce a severe behavioral disorder in those who are especially susceptible because of genetic or other factors, e.g., malnutrition. Third, for the child's parents or teachers, some metal induced behavioral effects (e.g., hyper- or hypo-irritability) may make a child difficult to care for or educate, leading to adult-child tensions that become amplified and aggravated over time.

It is also apparent that a blood lead level of 30 ug/dl does not constitute a safety limit as proposed by the United States Center for Disease Control, and, at the moment, there is no evidence that

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It is also apparent that a blood lead level of 30 ug/dl does not constitute a safety limit as proposed by the United States Center for Disease Control, and, at the moment, there is no evidence that

a threshold for lead exposure exists. Lansdown et al.'s /21/ findings show that around a mean level of 13 ug/dl there are significant emotional and behavioral differences between children with higher and lower lead levels. As such, preventive efforts directed toward reducing children's exposure to metal pollutants should be augmented on a high priority basis. The alternative in terms of metal pollutants continuing neurotoxic effects on children's central nervous system and behavioral performance is clearly unacceptable.

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